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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,470	08/16/2001	James M. Hagberg	108172-00071	6361

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EXAMINER
EINSMANN, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/06/2002 7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,470	HAGBERG ET AL.	
	Examiner	Art Unit	
	Juliet C Einsmann	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) *1 and 3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group 1, claim(s) 1, drawn to a method of improving cholesterol levels in a subject which comprises identifying a subject with a particular genotype for a glucose transport 4 gene.

Group 2, claim(s) 2 and 4, drawn to methods of improving cholesterol levels or diabetes status which comprise identifying a subject with a particular genotype for a myostatin exon 2 gene.

Group 3, claim(s) 3, drawn to methods for improving cholesterol levels which comprise identifying a subject with a particular genotype of an insulin receptor substrate-1 gene.

2. The inventions listed as Groups 1-3 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Each grouping is considered to have a different special technical feature because they are each drawn to methods which comprise steps of genotyping separate genes. Thus, for each grouping, the association between the particular recited genotypes and the methods for improvement is considered to be the special technical feature.

3. During a telephone conversation with Dan Dazara (47,543) on 5/6/02 a provisional election was made with traverse to prosecute the invention of group 2, claims 2 and 4. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1 and 3 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): The specification recites nucleic acid sequences, but there is no sequence listing or CRF on file. Further the sequences are not identified with proper sequence identifiers.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit a new CRF and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 4 are indefinite over the recitation of "having a "12" genotype" and "having a "11" genotype," respectively. The specification does not define these annotations to describe what a "11" genotype or a "12" genotype is, and thus, the method is unclear. The specification, at page 7 describes methods for the genotyping of the second exon of the myostatin gene, but the specification does not describe how this method relates to the designations "11" and "12." Thus, it is impossible to ascertain what genotype is being identified in claims 2 and 4.

Claims 2 and 4 are indefinite over the recitation "a myostatin exon 2 gene" because it is not clear if this refers to the second exon of the myostatin gene or if this refers to a different gene called the "myostatin exon 2" gene.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 2 and 4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 2 is drawn to a method of improving cholesterol levels in a subject in need of such improvement by identifying a subject with hypercholesteremia having a "12" genotype for a myostatin exon 2 gene and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

Claim 4 is drawn to a method for improving diabetes status in a subject by identifying a subject with diabetes having a "11" genotype for a myostatin exon 2 gene and engaging the

subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject.

As a first point, as noted in the rejections under 112 2nd paragraph, neither the specification nor the claims clearly set forth the meaning of the "11" or "12" genotypes, and thus, the methods of the instantly rejected claims are largely undefined. However, even if these genotypes were clearly defined, the specification is not enabling for the practice of the claimed methods.

The claimed methods both rely on the establishment of a relationship between particular alleles in the second exon of the myostatin gene and a particular phenotype (i.e. the ability to improve cholesterol levels with extensive exercise or the ability to improve diabetes status with extensive exercise). The prior art is silent with respect to polymorphisms in the human myostatin gene. However, the state of the art with regard to the establishment of such a relationship between a polymorphism and a phenotype is highly unpredictable. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis)

it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789).

The data in the specification highlight this unpredictability. With regard to methods for improving cholesterol status, the specification and claims assert that patients with a "12" genotype exhibit greater improvements after an extensive exercise routine for nine months. However, the data to support this assertion only represent three people total with the "12" genotype and the standard deviations in the data points given are nearly as large as the average values reported. No statistical analysis is provided, so it is unknown from the data whether a statistically significant correlation was observed. Certainly the ranges of improvement observed for patients with the "12" genotype versus the "11" genotype overlap when the standard deviations are considered. Thus, the data themselves demonstrate that it is not predictable, even once a genotype is observed which patients will exhibit an improvement even after nine months of an extensive exercise regime.

The data regarding an improvement in diabetes status also is widely variant and represents a small sample population. Again, no statistical analysis is presented to aid in the interpretation of the data. In light of these factors it is impossible to ascertain whether a reliable association has been demonstrated between nine months of an extensive exercise regime and an improvement in diabetes status correlated with a particular phenotype.

Furthermore, it is noted that the claims encompass "extensive exercise" for any length of time, yet the specification provides only a demonstration of the changes that occur after nine months of endurance exercise training. It is highly unpredictable as to what other shorter lengths

of training would be sufficient to improve cholesterol or diabetes status for patients having the "12" or "11" genotypes, as appropriate.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability, the lack of clearly defined and analyzed working examples, and the breadth of the claims, it is concluded that undue experimentation would be required to practice the claimed invention.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C. Einsmann
Examiner
Art Unit 1634

October 31, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600